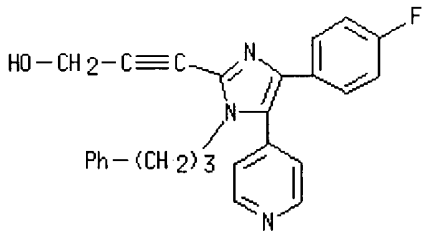
PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

L4 63 ANSWERS REGISTRY COPYRIGHT 2004 ACS on STN
IN 2-Propyn-1-ol, 3-[4-(4-fluorophenyl)-1-(3-phenylpropyl)-5-(4-pyridinyl)-1H-imidazol-2-yl]- (9CI)
MF C26 H22 F N3 O

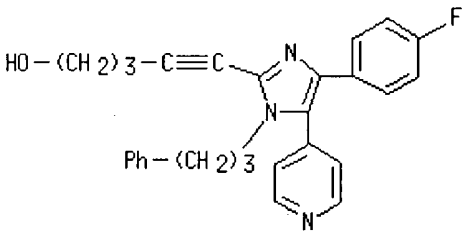
C2 129.03302 8
103 (a) Nomalogue



Ca 129:330728

PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

L4 63 ANSWERS REGISTRY COPYRIGHT 2004 ACS on STN
IN 4-Pentyn-1-ol, 5-[4-(4-fluorophenyl)-1-(3-phenylpropyl)-5-(4-pyridinyl)-1H-imidazol-2-yl]- (9CI)
MF C28 H26 F N3 O



103 (a) pomwoko

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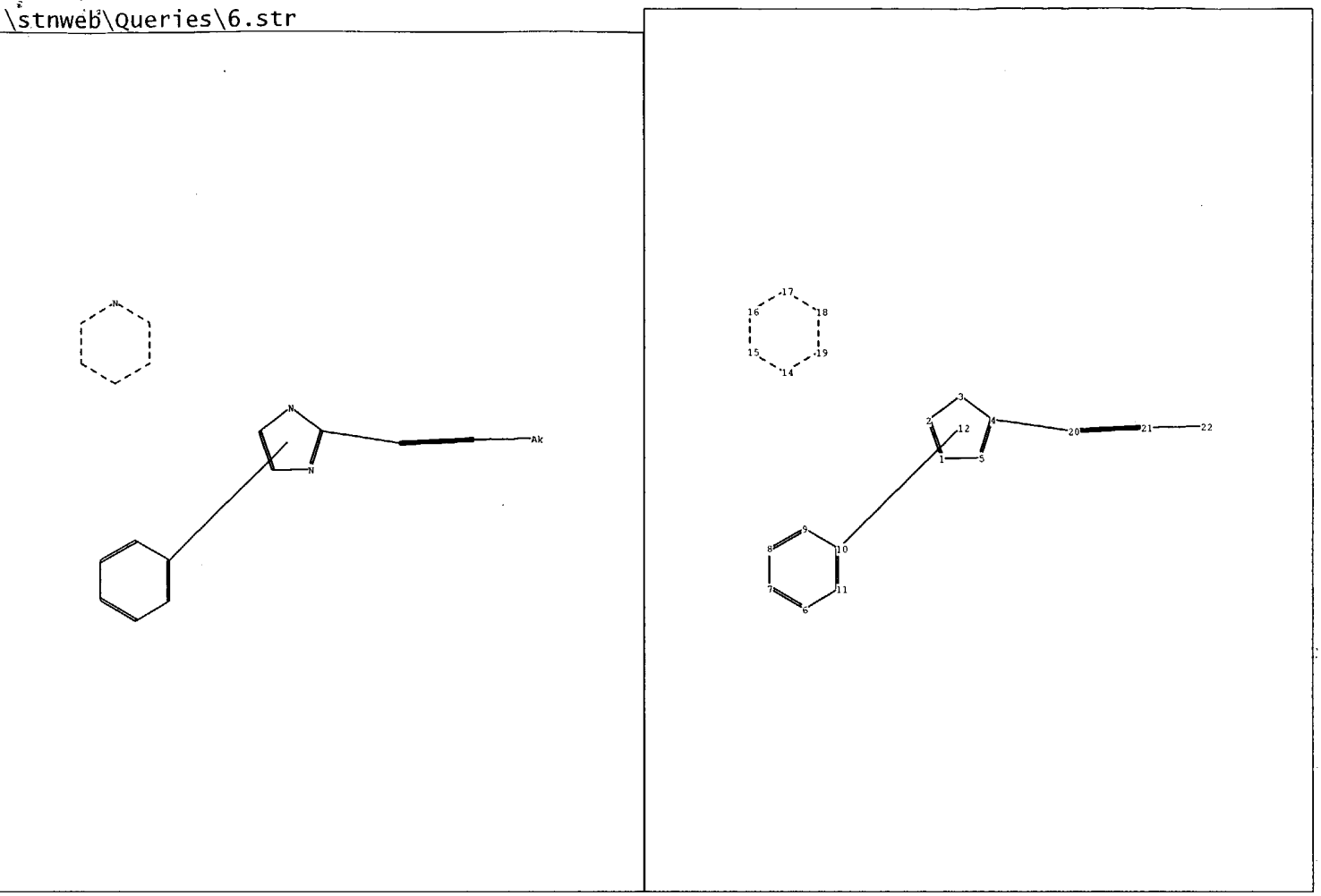

ain nodes :
20 21 22
ng nodes :
1 2 3 4 5 6 7 8 9 10 11 14 15 16 17 18 19
ain bonds :
4-20 20-21 21-22
ng bonds :
1-2 1-5 2-3 3-4 4-5 6-7 6-11 7-8 8-9 9-10 10-11 14-15 14-19 15-16 16-17
17-18 18-19
act/norm bonds :
1-5 2-3 3-4 4-5 14-15 14-19 15-16 16-17 17-18 18-19 21-22
act bonds :
1-2 4-20 20-21
rmalized bonds :
6-7 6-11 7-8 8-9 9-10 10-11
olated ring systems :
containing 1 : 6 : 14 :

tch level :
1:Atom 2:Atom 3:Atom 4:Atom 5:Atom 6:Atom 7:Atom 8:Atom 9:Atom 10:Atom 11:Atom
12:CLASS 14:Atom 15:Atom 16:Atom 17:Atom 18:Atom 19:Atom 20:CLASS 21:CLASS
22:CLASS

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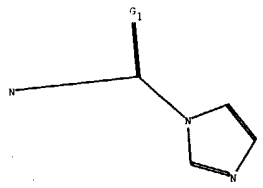

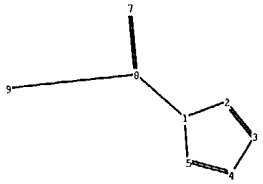

```
ain nodes :
   7  8  9
ng nodes :
   1  2  3  4  5
ain bonds :
   1-8  7-8  8-9
ng bonds :
   1-2  1-5  2-3  3-4  4-5
xact/norm bonds :
   1-2  1-5  1-8  3-4  4-5  7-8  8-9
xact bonds :
   2-3
olated ring systems :
   containing 1 :


:O,S

tch level :
   1:Atom  2:Atom  3:Atom  4:Atom  5:Atom  7:CLASS  8:CLASS  9:CLASS
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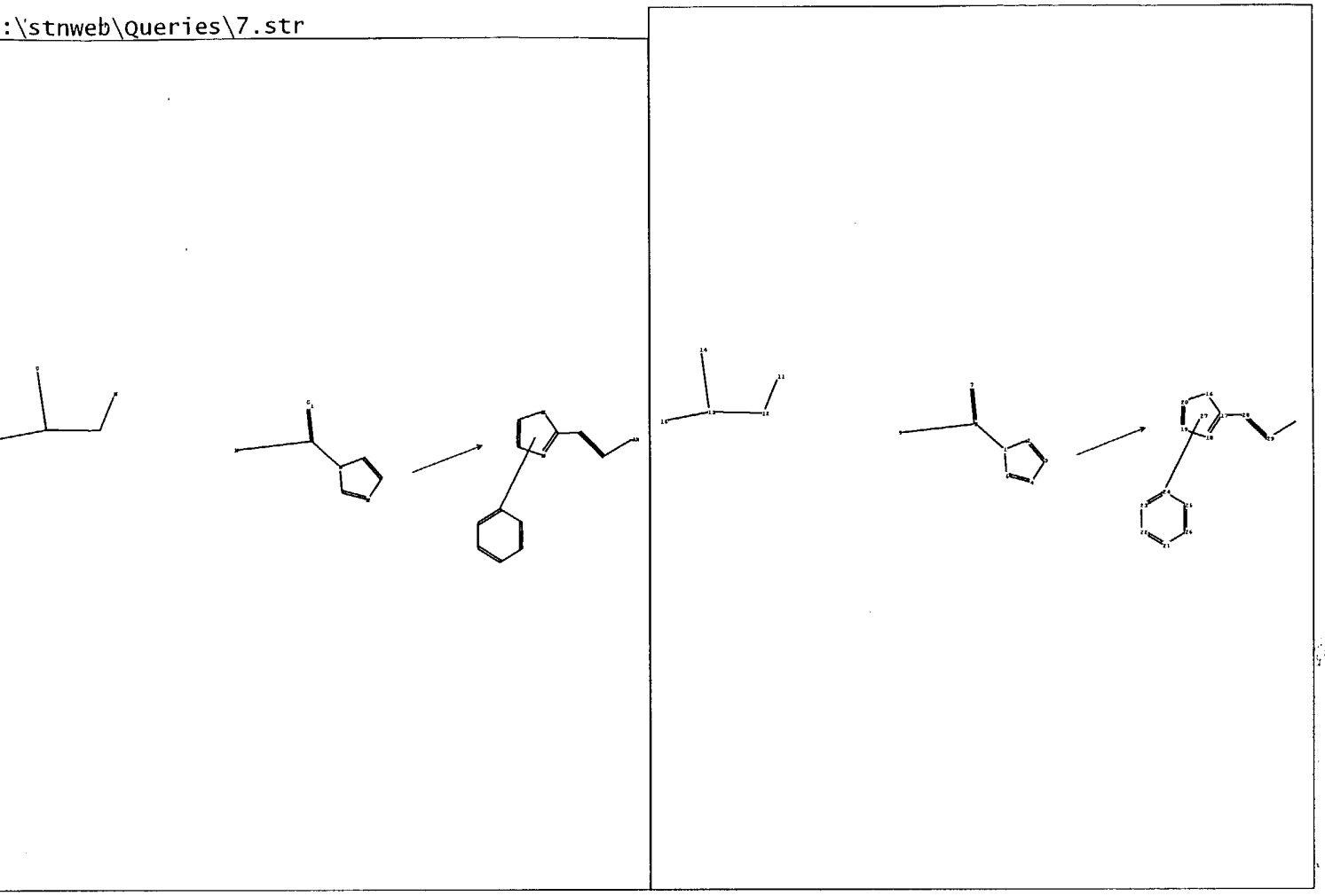
:\stnweb\Queries\7.str



hain nodes :
7 8 9 11 12 13 14 15 28 29 30
ing nodes :
1 2 3 4 5 16 17 18 19 20 21 22 23 24 25 26
hain bonds :
1-8 7-8 8-9 11-12 12-13 13-15 13-14 17-28 28-29 29-30
ing bonds :
1-2 1-5 2-3 3-4 4-5 16-17 16-20 17-18 18-19 19-20 21-22 21-26 22-23 23-24
24-25 25-26
xact/norm bonds :
1-2 1-5 1-8 3-4 4-5 7-8 8-9 11-12 13-15 13-14 16-17 16-20 17-18 18-19 29-30
xact bonds :
2-3 12-13 17-28 19-20 28-29
ormalized bonds :
21-22 21-26 22-23 23-24 24-25 25-26
solated ring systems :
containing 1 : 16 : 21 :

1:O,S

atch level :
1:Atom 2:Atom 3:Atom 4:Atom 5:Atom 7:CLASS 8:CLASS 9:CLASS 11:CLASS 12:CLASS
13:CLASS 14:CLASS 15:CLASS 16:Atom 17:Atom 18:Atom 19:Atom 20:Atom 21:Atom
22:Atom 23:Atom 24:Atom 25:Atom 26:Atom 27:CLASS 28:CLASS 29:CLASS 30:CLASS
ragments assigned reactant role:
containing 1
containing 11
ragments assigned product role:
containing 16

```
* * * * * * * * * *   Welcome to STN International   * * * * * * * * * *

 NEWS  1           Web Page URLs for STN Seminar Schedule - N. America
 NEWS  2           "Ask CAS" for self-help around the clock
 NEWS  3  May 10   PROUSDDR now available on STN
 NEWS  4  May 19   PROUSDDR: One FREE connect hour, per account, in both May
                   and June 2004
 NEWS  5  May 12   EXTEND option available in structure searching
 NEWS  6  May 12   Polymer links for the POLYLINK command completed in REGISTRY
 NEWS  7  May 17   FRFULL now available on STN
 NEWS  8  May 27   New UPM (Update Code Maximum) field for more efficient patent
                   SDIs in CAplus
 NEWS  9  May 27   CAplus super roles and document types searchable in REGISTRY
 NEWS 10  May 27   Explore APOLLIT with free connect time in June 2004
 NEWS 11  Jun 22   STN Patent Forums to be held July 19-22, 2004
 NEWS 12  Jun 28   Additional enzyme-catalyzed reactions added to CASREACT
 NEWS 13  Jun 28   ANTE, AQUALINE, BIOENG, CIVILENG, ENVIROENG, MECHENG,
                   and WATER from CSA now available on STN(R)

 NEWS EXPRESS  MARCH 31 CURRENT WINDOWS VERSION IS V7.00A, CURRENT
               MACINTOSH VERSION IS V6.0c(ENG) AND V6.0Jc(JP),
               AND CURRENT DISCOVER FILE IS DATED 26 APRIL 2004
 NEWS HOURS    STN Operating Hours Plus Help Desk Availability
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 NEWS PHONE    Direct Dial and Telecommunication Network Access to STN
 NEWS WWW      CAS World Wide Web Site (general information)

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  * * * * * * * * * * * * * * * STN  Columbus  * * * * * * * * * * * * * * *

FILE 'HOME' ENTERED AT 20:05:13 ON 01 JUL 2004

=> file reg
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                       ENTRY    SESSION
FULL ESTIMATED COST                                     0.21       0.21

FILE 'REGISTRY' ENTERED AT 20:05:21 ON 01 JUL 2004
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STRUCTURE FILE UPDATES:   30 JUN 2004  HIGHEST RN 701907-96-2
DICTIONARY FILE UPDATES:  30 JUN 2004  HIGHEST RN 701907-96-2

TSCA INFORMATION NOW CURRENT THROUGH JANUARY 6, 2004

  Please note that search-term pricing does apply when
```

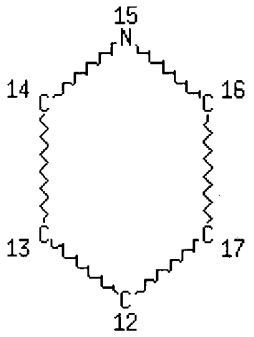
conducting SmartSELECT searches.

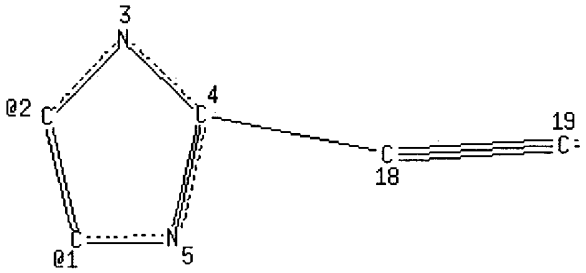
Crossover limits have been increased. See HELP CROSSOVER for details.

Experimental and calculated property data are now available. For more information enter HELP PROP at an arrow prompt in the file or refer to the file summary sheet on the web at:
http://www.cas.org/ONLINE/DBSS/registryss.html

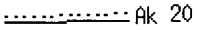
=>
L1 STRUCTURE UPLOADED

=> d l1
L1 HAS NO ANSWERS
L1 STR

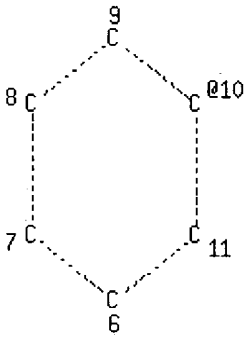




Page 1-A



Page 1-B



Page 2-A
VPA 10-1/2 S
NODE ATTRIBUTES:
NSPEC IS R AT 1
NSPEC IS R AT 2
NSPEC IS R AT 3
NSPEC IS R AT 4
NSPEC IS R AT 5
NSPEC IS R AT 6

```
NSPEC   IS R      AT   7
NSPEC   IS R      AT   8
NSPEC   IS R      AT   9
NSPEC   IS R      AT  10
NSPEC   IS R      AT  11
NSPEC   IS R      AT  12
NSPEC   IS R      AT  13
NSPEC   IS R      AT  14
NSPEC   IS R      AT  15
NSPEC   IS R      AT  16
NSPEC   IS R      AT  17
NSPEC   IS C      AT  18
NSPEC   IS C      AT  19
NSPEC   IS C      AT  20
DEFAULT MLEVEL IS ATOM
MLEVEL  IS CLASS  AT  18 19 20
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RSPEC I
NUMBER OF NODES IS  20

STEREO ATTRIBUTES: NONE


=> s l1
SAMPLE SEARCH INITIATED 20:06:06 FILE 'REGISTRY'
SAMPLE SCREEN SEARCH COMPLETED -     90 TO ITERATE

100.0% PROCESSED      90 ITERATIONS                          2 ANSWERS
SEARCH TIME: 00.00.01

FULL FILE PROJECTIONS:  ONLINE  **COMPLETE**
                        BATCH   **COMPLETE**
PROJECTED ITERATIONS:         1231 TO     2369
PROJECTED ANSWERS:               2 TO      124

L2            2 SEA SSS SAM L1

=> s l1 full
THE ESTIMATED SEARCH COST FOR FILE 'REGISTRY' IS 155.00 U.S. DOLLARS
DO YOU WANT TO CONTINUE WITH THIS REQUEST? (Y)/N or END:y
FULL SEARCH INITIATED 20:06:10 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED -   1628 TO ITERATE

100.0% PROCESSED    1628 ITERATIONS                         35 ANSWERS
SEARCH TIME: 00.00.01

L3           35 SEA SSS FUL L1

=> file hcaplus
COST IN U.S. DOLLARS                          SINCE FILE      TOTAL
                                                 ENTRY    SESSION
FULL ESTIMATED COST                              155.84     156.05

FILE 'HCAPLUS' ENTERED AT 20:06:16 ON 01 JUL 2004
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```

FILE COVERS 1907 - 1 Jul 2004 VOL 141 ISS 1
FILE LAST UPDATED: 30 Jun 2004 (20040630/ED)

This file contains CAS Registry Numbers for easy and accurate
substance identification.

```
=> s l3/prep
            16 L3
       3166075 PREP/RL
L4            2 L3/PREP
                (L3 (L) PREP/RL)

=> file reg
COST IN U.S. DOLLARS                          SINCE FILE      TOTAL
                                                   ENTRY    SESSION
FULL ESTIMATED COST                                2.36     158.41

FILE 'REGISTRY' ENTERED AT 20:06:35 ON 01 JUL 2004
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STRUCTURE FILE UPDATES:   30 JUN 2004  HIGHEST RN 701907-96-2
DICTIONARY FILE UPDATES:  30 JUN 2004  HIGHEST RN 701907-96-2

TSCA INFORMATION NOW CURRENT THROUGH JANUARY 6, 2004

  Please note that search-term pricing does apply when
  conducting SmartSELECT searches.

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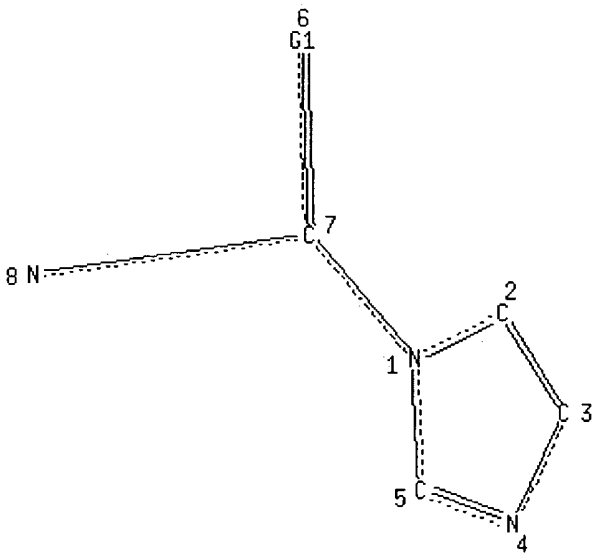
Experimental and calculated property data are now available. For more
information enter HELP PROP at an arrow prompt in the file or refer
to the file summary sheet on the web at:
http://www.cas.org/ONLINE/DBSS/registryss.html

=>
L5       STRUCTURE UPLOADED

=> d l5
L5 HAS NO ANSWERS
L5              STR
 0 9  S 10
Page 1-A
```



Page 1-B
VAR G1=9/10
NODE ATTRIBUTES:
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NSPEC IS R AT 2
NSPEC IS R AT 3
NSPEC IS R AT 4
NSPEC IS R AT 5
NSPEC IS C AT 6
NSPEC IS C AT 7
NSPEC IS C AT 8
DEFAULT MLEVEL IS ATOM
MLEVEL IS CLASS AT 7 8 9 10
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RSPEC I
NUMBER OF NODES IS 10

STEREO ATTRIBUTES: NONE

=> s l5
SAMPLE SEARCH INITIATED 20:08:50 FILE 'REGISTRY'
SAMPLE SCREEN SEARCH COMPLETED - 582 TO ITERATE

100.0% PROCESSED 582 ITERATIONS 50 ANSWERS
INCOMPLETE SEARCH (SYSTEM LIMIT EXCEEDED)
SEARCH TIME: 00.00.01

FULL FILE PROJECTIONS: ONLINE **COMPLETE**
BATCH **COMPLETE**
PROJECTED ITERATIONS: 10193 TO 13087
PROJECTED ANSWERS: 2038 TO 3442

L6 50 SEA SSS SAM L5

=> s l5 full
THE ESTIMATED SEARCH COST FOR FILE 'REGISTRY' IS 155.00 U.S. DOLLARS
DO YOU WANT TO CONTINUE WITH THIS REQUEST? (Y)/N or END:y
FULL SEARCH INITIATED 20:08:55 FILE 'REGISTRY'

```
FULL SCREEN SEARCH COMPLETED -  12539 TO ITERATE

100.0% PROCESSED   12539 ITERATIONS                          2876 ANSWERS
SEARCH TIME: 00.00.01

L7         2876 SEA SSS FUL L5

=> file hcaplus
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                       ENTRY    SESSION
FULL ESTIMATED COST                                   156.68     315.09

FILE 'HCAPLUS' ENTERED AT 20:08:58 ON 01 JUL 2004
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FILE COVERS 1907 - 1 Jul 2004  VOL 141 ISS 1
FILE LAST UPDATED: 30 Jun 2004  (20040630/ED)

 This file contains CAS Registry Numbers for easy and accurate
 substance identification.


=> s l7
L8         1663 L7

=> s l7/rct
           1663 L7
        2635540 RCT/RL
L9          249 L7/RCT
                  (L7 (L) RCT/RL)

=> d his

     (FILE 'HOME' ENTERED AT 20:05:13 ON 01 JUL 2004)

     FILE 'REGISTRY' ENTERED AT 20:05:21 ON 01 JUL 2004
L1                STRUCTURE UPLOADED
L2              2 S L1
L3             35 S L1 FULL

     FILE 'HCAPLUS' ENTERED AT 20:06:16 ON 01 JUL 2004
L4              2 S L3/PREP

     FILE 'REGISTRY' ENTERED AT 20:06:35 ON 01 JUL 2004
L5                STRUCTURE UPLOADED
L6             50 S L5
L7           2876 S L5 FULL
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     FILE 'HCAPLUS' ENTERED AT 20:08:58 ON 01 JUL 2004
L8          1663 S L7
L9           249 S L7/RCT

=> s l9 and l4
L10            1 L9 AND L4

=> d l10, ibib abs hitstr, 1

L10  ANSWER 1 OF 1  HCAPLUS  COPYRIGHT 2004 ACS on STN
```

Full Text | Citing References

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ACCESSION NUMBER:          2002:754379  HCAPLUS
DOCUMENT NUMBER:           137:263034
TITLE:                     Process for the preparation of tetrasubstituted
                           imidazole derivatives and novel crystalline structures
                           thereof
INVENTOR(S):               Zhong, Hua; Dubberke, Silke; Muller, Stefan; Rossler,
                           Armin; Schultz, Thomas W.; Korey, Daniel J.; Otten,
                           Thomas; Walker, Donald G.; Abdel-Magid, Abdel
PATENT ASSIGNEE(S):        Ortho-Mcneil Pharmaceutical, Inc., USA
SOURCE:                    PCT Int. Appl., 55 pp.
                           CODEN: PIXXD2
DOCUMENT TYPE:             Patent
LANGUAGE:                  English
FAMILY ACC. NUM. COUNT:    1
PATENT INFORMATION:

     PATENT NO.         KIND  DATE          APPLICATION NO.  DATE
     ---------------    ----  --------      ---------------  --------
     WO 2002076974      A2    20021003      WO 2002-US5419   20020222
     WO 2002076974      A3    20030213
         W:  AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,
             CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,
             GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,
             LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH,
             PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ,
             UA, UG, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
         RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH,
             CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR,
             BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG
     US 2003045723      A1    20030306      US 2002-81553    20020222
     BR 2002008462      A     20040302      BR 2002-8462     20020222
     EP 1392678         A2    20040303      EP 2002-753758   20020222
         R:  AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
             IE, SI, LT, LV, FI, RO, MK, CY, AL, TR
PRIORITY APPLN. INFO.:                     US 2001-278607P  P  20010326
                                           US 2002-81553    A  20020222
                                           WO 2002-US5419   W  20020222
OTHER SOURCE(S):           CASREACT 137:263034; MARPAT 137:263034
GI
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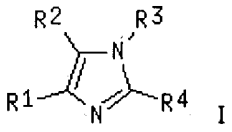
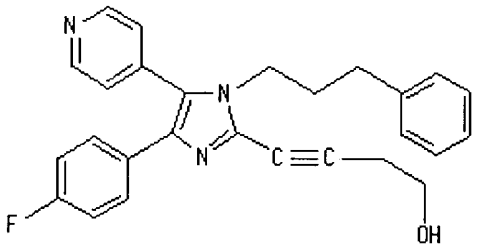


I



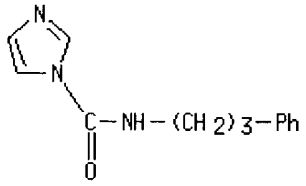
II

AB The present invention relates to a process for the prepn. of I [R1 = (un)substituted Ph; R2 = (un)substituted phenyl; R3 = H, aryl; R4 = C≡C(CH2)0-9-X; X = H, OH, vinyl, etc.]. For instance, the dimethoxy acetal of 4-pyridinecarboxaldehyde was lithiated (THF, n-BuLi, -15°) and added to the N-TMS-imine deriv. of 4-fluorobenzaldehyde (prepn. given) to afford 2,2-Dimethoxy-2-(4-pyridyl)-1-(4-fluorophenyl)ethanamine in 79% yield. This intermediate was acylated with N-(3-phenylpropyl)-1H-imidazole-1-carboxamide (prepn. given), to give the corresponding urea. This was treated with formic acid at 95-100° for 24 h resulting in hydrolysis of the ketal with concomitant cyclization to the corresponding imidazolin-2-one. The imidazolin-2-one was converted to the bromide (sulfolane, POBr3, 130°, 3 h, 62%) and subsequently coupled to 3-butyn-1-ol to give II in 75% yield. Two polymorphs of II were characterized by XRPD.

IT **149047-40-5P**, N-(3-Phenylpropyl)-1H-imidazole-1-carboxamide
RL: **RCT (Reactant)**; SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(intermediate; process for prepn. of tetrasubstituted imidazole derivs. and novel cryst. structures thereof)

RN 149047-40-5 HCAPLUS

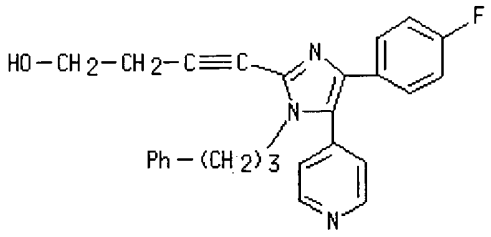
CN 1H-Imidazole-1-carboxamide, N-(3-phenylpropyl)- (9CI) (CA INDEX NAME)



IT **215303-72-3P**, 4-(4-Fluorophenyl)-2-(4-hydroxy-1-butynyl)-1-(3-Phenylpropyl)-5-(4-Pyridyl)imidazole
RL: SPN (Synthetic preparation); **PREP (Preparation)**
(process for prepn. of tetrasubstituted imidazole derivs. and novel cryst. structures thereof)

RN 215303-72-3 HCAPLUS

CN 3-Butyn-1-ol, 4-[4-(4-fluorophenyl)-1-(3-phenylpropyl)-5-(4-pyridinyl)-1H-imidazol-2-yl]- (9CI) (CA INDEX NAME)

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=> file caold
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                       ENTRY    SESSION
FULL ESTIMATED COST                                     7.12     322.21

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)          SINCE FILE      TOTAL
                                                       ENTRY    SESSION
CA SUBSCRIBER PRICE                                    -0.69      -0.69

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FILE COVERS 1907-1966
FILE LAST UPDATED:  01 May 1997 (19970501/UP)

  This file contains CAS Registry Numbers for easy and accurate
  substance identification.  Title keywords, authors, patent
  assignees, and patent information, e.g., patent numbers, are
  now searchable from 1907-1966.  TIFF images of CA abstracts
  printed between 1907-1966 are available in the PAGE
  display formats.

  This file supports REG1stRY for direct browsing and searching of
  all substance data from the REGISTRY file.  Enter HELP FIRST for
  more information.

=> d his

     (FILE 'HOME' ENTERED AT 20:05:13 ON 01 JUL 2004)

     FILE 'REGISTRY' ENTERED AT 20:05:21 ON 01 JUL 2004
L1              STRUCTURE UPLOADED
L2            2 S L1
L3           35 S L1 FULL

     FILE 'HCAPLUS' ENTERED AT 20:06:16 ON 01 JUL 2004
L4            2 S L3/PREP

     FILE 'REGISTRY' ENTERED AT 20:06:35 ON 01 JUL 2004
L5              STRUCTURE UPLOADED
L6           50 S L5
L7         2876 S L5 FULL

     FILE 'HCAPLUS' ENTERED AT 20:08:58 ON 01 JUL 2004
L8         1663 S L7
L9          249 S L7/RCT
L10           1 S L9 AND L4
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     FILE 'CAOLD' ENTERED AT 20:09:33 ON 01 JUL 2004

=> s l3 and l7
                  0 L3
            25 L7
L11           0 L3 AND L7

=> file casreact
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                         ENTRY    SESSION
FULL ESTIMATED COST                                       0.84     323.05

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)          SINCE FILE      TOTAL
                                                         ENTRY    SESSION
CA SUBSCRIBER PRICE                                       0.00      -0.69

FILE 'CASREACT' ENTERED AT 20:10:37 ON 01 JUL 2004
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FILE CONTENT:1840 - 27 Jun 2004 VOL 140 ISS 26

************************************************************
*                                                          *
*     CASREACT now has more than  8 million reactions      *
*                                                          *
************************************************************

Some records from 1974 to 1991 are derived from the ZIC/VINITI data file
and provided by InfoChem and some records are produced using some INPI
data from the period prior to 1986.  Biotransformations database from
(1971-1998).

This file contains CAS Registry Numbers for easy and accurate substance
identification.

=>
L12     STRUCTURE UPLOADED

=> d l12
L12 HAS NO ANSWERS
L12             STR

=> s l12
SAMPLE SEARCH INITIATED 20:14:58 FILE 'CASREACT'
SCREENING COMPLETE -      0 REACTIONS TO VERIFY FROM      0 DOCUMENTS

100.0% DONE      0 VERIFIED       0 HIT RXNS                     0 DOCS
SEARCH TIME: 00.00.01

FULL FILE PROJECTIONS:  ONLINE  **COMPLETE**
                        BATCH   **COMPLETE**
PROJECTED VERIFICATIONS:          0 TO        0
PROJECTED ANSWERS:                0 TO        0
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```
L13             0 SEA SSS SAM L12 (      0 REACTIONS)

=> s l12 full
THE ESTIMATED SEARCH COST FOR FILE 'CASREACT' IS 102.30 U.S. DOLLARS
DO YOU WANT TO CONTINUE WITH THIS REQUEST? (Y)/N or END:y
FULL SEARCH INITIATED 20:15:03 FILE 'CASREACT'
SCREENING COMPLETE -       0 REACTIONS TO VERIFY FROM       0 DOCUMENTS

100.0% DONE       0 VERIFIED        0 HIT RXNS                        0 DOCS
SEARCH TIME: 00.00.01

L14             0 SEA SSS FUL L12 (      0 REACTIONS)

=> log y
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                       ENTRY    SESSION
FULL ESTIMATED COST                                   105.66     428.71

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)          SINCE FILE      TOTAL
                                                       ENTRY    SESSION
CA SUBSCRIBER PRICE                                     0.00      -0.69

STN INTERNATIONAL LOGOFF AT 20:15:15 ON 01 JUL 2004
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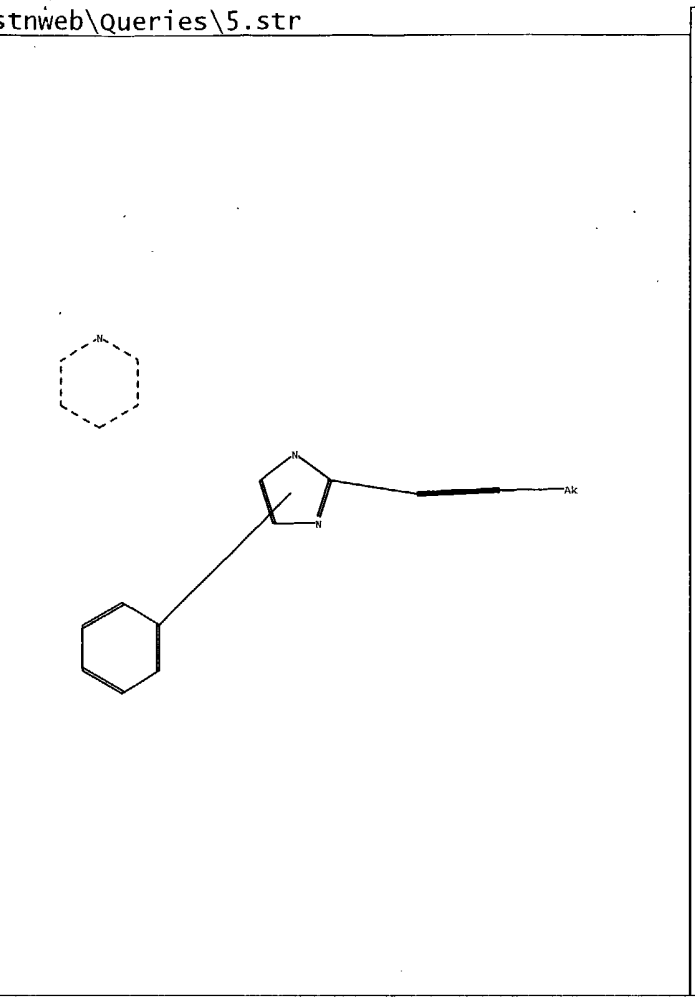
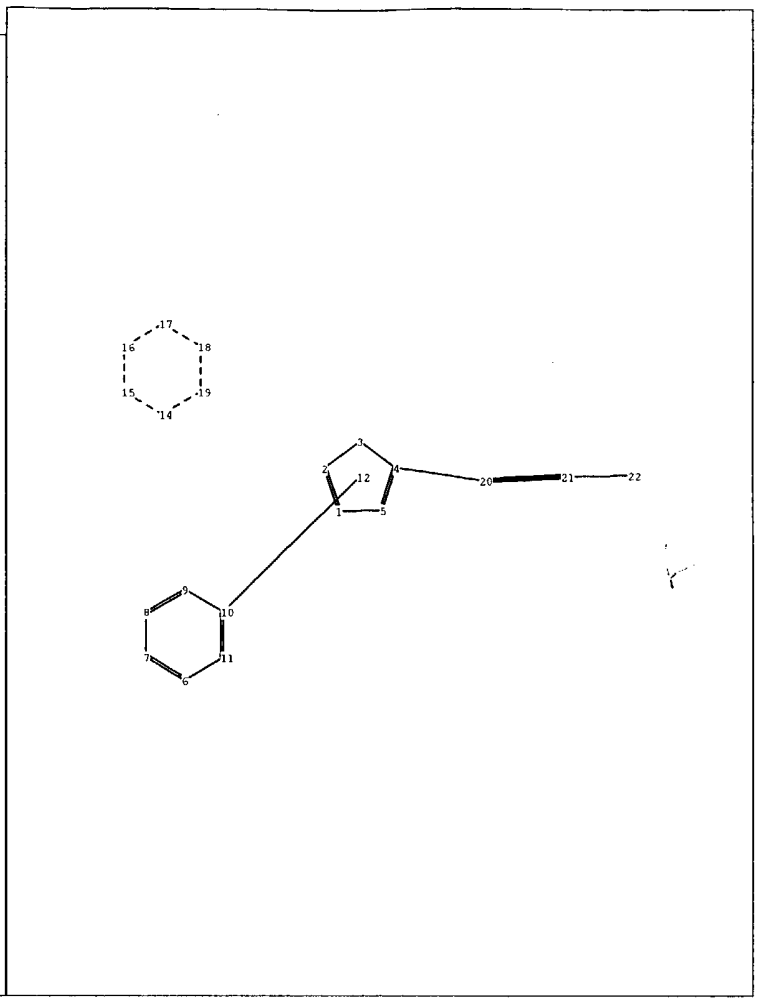
stnweb\Queries\5.str





n nodes :
20 21 22
g nodes :
1 2 3 4 5 6 7 8 9 10 11 14 15 16 17 18 19
n bonds :
4-20 20-21 21-22
g bonds :
1-2 1-5 2-3 3-4 4-5 6-7 6-11 7-8 8-9 9-10 10-11 14-15 14-19 15-16 16-17
17-18 18-19
ct/norm bonds :
1-5 2-3 3-4 4-5 14-15 14-19 15-16 16-17 17-18 18-19 21-22
ct bonds :
1-2 4-20 20-21
malized bonds :
6-7 6-11 7-8 8-9 9-10 10-11
ated ring systems :
containing 1 : 6 : 14 :

th level :
1:Atom 2:Atom 3:Atom 4:Atom 5:Atom 6:Atom 7:Atom 8:Atom 9:Atom 10:Atom 11:Atom
12:CLASS 14:Atom 15:Atom 16:Atom 17:Atom 18:Atom 19:Atom 20:CLASS 21:CLASS
22:CLASS

```
* * * * * * * * * *   Welcome to STN International   * * * * * * * * * *

 NEWS  1           Web Page URLs for STN Seminar Schedule - N. America
 NEWS  2           "Ask CAS" for self-help around the clock
 NEWS  3  May 10   PROUSDDR now available on STN
 NEWS  4  May 19   PROUSDDR: One FREE connect hour, per account, in both May
                   and June 2004
 NEWS  5  May 12   EXTEND option available in structure searching
 NEWS  6  May 12   Polymer links for the POLYLINK command completed in REGISTRY
 NEWS  7  May 17   FRFULL now available on STN
 NEWS  8  May 27   New UPM (Update Code Maximum) field for more efficient patent
                   SDIs in CAplus
 NEWS  9  May 27   CAplus super roles and document types searchable in REGISTRY
 NEWS 10  May 27   Explore APOLLIT with free connect time in June 2004
 NEWS 11  Jun 22   STN Patent Forums to be held July 19-22, 2004
 NEWS 12  Jun 28   Additional enzyme-catalyzed reactions added to CASREACT
 NEWS 13  Jun 28   ANTE, AQUALINE, BIOENG, CIVILENG, ENVIROENG, MECHENG,
                   and WATER from CSA now available on STN(R)

 NEWS EXPRESS  MARCH 31 CURRENT WINDOWS VERSION IS V7.00A, CURRENT
               MACINTOSH VERSION IS V6.0c(ENG) AND V6.0Jc(JP),
               AND CURRENT DISCOVER FILE IS DATED 26 APRIL 2004
 NEWS HOURS    STN Operating Hours Plus Help Desk Availability
 NEWS INTER    General Internet Information
 NEWS LOGIN    Welcome Banner and News Items
 NEWS PHONE    Direct Dial and Telecommunication Network Access to STN
 NEWS WWW      CAS World Wide Web Site (general information)

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FILE 'HOME' ENTERED AT 19:45:07 ON 01 JUL 2004

=> file reg
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                      ENTRY    SESSION
FULL ESTIMATED COST                                    0.21       0.21

FILE 'REGISTRY' ENTERED AT 19:45:15 ON 01 JUL 2004
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STRUCTURE FILE UPDATES:   30 JUN 2004  HIGHEST RN 701907-96-2
DICTIONARY FILE UPDATES:  30 JUN 2004  HIGHEST RN 701907-96-2

TSCA INFORMATION NOW CURRENT THROUGH JANUARY 6, 2004

  Please note that search-term pricing does apply when
```

conducting SmartSELECT searches.

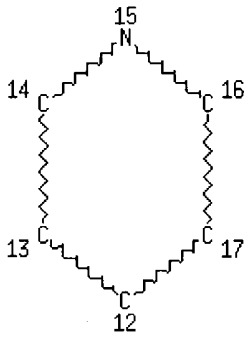
Crossover limits have been increased. See HELP CROSSOVER for details.

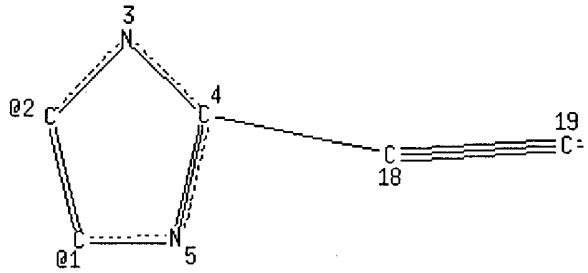
Experimental and calculated property data are now available. For more information enter HELP PROP at an arrow prompt in the file or refer to the file summary sheet on the web at:
http://www.cas.org/ONLINE/DBSS/registryss.html

=>
L1 STRUCTURE UPLOADED

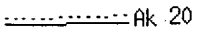
=> l1
L1 IS NOT A RECOGNIZED COMMAND
The previous command name entered was not recognized by the system.
For a list of commands available to you in the current file, enter
"HELP COMMANDS" at an arrow prompt (=>).

=> d l1
L1 HAS NO ANSWERS
L1 STR

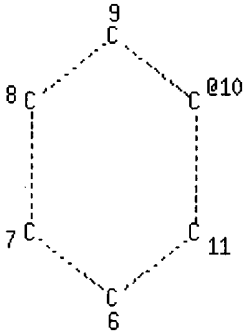




Page 1-A



Page 1-B



Page 2-A
VPA 10-1/2 S
NODE ATTRIBUTES:

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NSPEC   IS R      AT   2
NSPEC   IS R      AT   3
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NSPEC   IS R      AT   5
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NSPEC   IS R      AT  17
NSPEC   IS C      AT  18
NSPEC   IS C      AT  19
NSPEC   IS C      AT  20
DEFAULT MLEVEL IS ATOM
MLEVEL  IS CLASS  AT  18 19 20
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RSPEC I
NUMBER OF NODES IS  20

STEREO ATTRIBUTES: NONE


=> s l1
SAMPLE SEARCH INITIATED 19:48:58 FILE 'REGISTRY'
SAMPLE SCREEN SEARCH COMPLETED -     90 TO ITERATE

100.0% PROCESSED      90 ITERATIONS                              2 ANSWERS
SEARCH TIME: 00.00.01

FULL FILE PROJECTIONS:  ONLINE  **COMPLETE**
                        BATCH   **COMPLETE**
PROJECTED ITERATIONS:         1231 TO     2369
PROJECTED ANSWERS:               2 TO      124

L2            2 SEA SSS SAM L1

=> s l1 full
THE ESTIMATED SEARCH COST FOR FILE 'REGISTRY' IS 155.00 U.S. DOLLARS
DO YOU WANT TO CONTINUE WITH THIS REQUEST? (Y)/N or END:y
FULL SEARCH INITIATED 19:49:02 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED -   1628 TO ITERATE

100.0% PROCESSED    1628 ITERATIONS                             35 ANSWERS
SEARCH TIME: 00.00.01

L3           35 SEA SSS FUL L1

=> file hcaplus
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                       ENTRY    SESSION
FULL ESTIMATED COST                                   157.52     157.73
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FILE 'HCAPLUS' ENTERED AT 19:49:05 ON 01 JUL 2004
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FILE COVERS 1907 - 1 Jul 2004  VOL 141 ISS 1
FILE LAST UPDATED: 30 Jun 2004  (20040630/ED)

 This file contains CAS Registry Numbers for easy and accurate
 substance identification.


=> s l3
L4           16 L3

=> s l4 and burnett, d?/au
            392 BURNETT, D?/AU
L5            0 L4 AND BURNETT, D?/AU

=> s l4 and caplen, m?/au
             12 CAPLEN, M?/AU
L6            0 L4 AND CAPLEN, M?/AU

=> s l4 and czarniecki, m?/au
             50 CZARNIECKI, M?/AU
L7            0 L4 AND CZARNIECKI, M?/AU

=> s l4 and domalksi, m?/au
              0 DOMALKSI, M?/AU
L8            0 L4 AND DOMALKSI, M?/AU

=> s l4 and ho, g?/au
            280 HO, G?/AU
L9            0 L4 AND HO, G?/AU

=> s tulshian, d?/au
L10          46 TULSHIAN, D?/AU

=> s l10 and l4
L11           0 L10 AND L4

=> s l4 and wu, w?/au
           5877 WU, W?/AU
L12           2 L4 AND WU, W?/AU

=> d l12, ibib abs fhitstr, 1-2

L12  ANSWER 1 OF 2  HCAPLUS  COPYRIGHT 2004 ACS on STN
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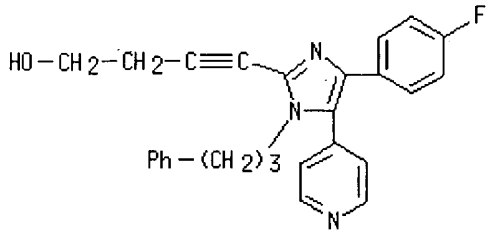
Full Text | Citing References

ACCESSION NUMBER: 1999:714273 HCAPLUS
DOCUMENT NUMBER: 132:30503
TITLE: RWJ 67657, a potent, orally active inhibitor of p38 mitogen-activated protein kinase
AUTHOR(S): Wadsworth, Scott A.; Cavender, Druie E.; Beers, Scott A.; Lalan, Praful; Schafer, Peter H.; Malloy, Elizabeth A.; **Wu, Wei**; Fahmy, Bohumila; Olini, Gilbert C.; Davis, Janet E.; Pellegrino-Gensey, J. Lee; Wachter, Michael P.; Siekierka, John J.
CORPORATE SOURCE: Drug Discovery, The R. W. Johnson Pharmaceutical Research Institute, Raritan, NJ, USA
SOURCE: Journal of Pharmacology and Experimental Therapeutics (1999), 291(2), 680-687
CODEN: JPETAB; ISSN: 0022-3565
PUBLISHER: American Society for Pharmacology and Experimental Therapeutics
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Tumor necrosis factor-α (TNF-α), a cytokine secreted by activated monocytes/macrophages and T lymphocytes, has been implicated in several disease states, including rheumatoid arthritis, inflammatory bowel disease, septic shock, and osteoporosis. Monocyte/macrophage prodn. of TNF-α is dependent on the mitogen-activated protein kinase p38. RWJ 67657 (4-[4-(4-fluorophenyl)-1-(3-phenylpropyl)-5-(4-pyridinyl)-1H-imidazol -2-yl]-3-butyn-1-ol) inhibited the release of TNF-α by lipopolysaccharide (a monocyte stimulus)-treated human peripheral blood mononuclear cells with an IC50 of 3 nM, as well as the release of TNF-α from peripheral blood mononuclear cells treated with the superantigen staphylococcal enterotoxin B (a T cell stimulus), with an IC50 value of 13 nM. This compd. was approx. 10-fold more potent than the literature std. p38 kinase inhibitor SB 203580 in all p38 dependent in vitro systems tested. RWJ 67657 inhibited the enzymic activity of recombinant p38α and β, but not γ or δ, in vitro and had no significant activity against a variety of other enzymes. In contrast, SB 203580 significantly inhibited the tyrosine kinases p56 lck and c-src (IC50 = 5 μM). RWJ 67657 did not inhibit T cell prodn. of interleukin-2 or interferon-γ and did not inhibit T cell proliferation in response to mitogens. RWJ 67657 inhibited TNF-α prodn. in lipopolysaccharide-injected mice (87% inhibition at 50 mg/kg) and in rats (91% inhibition at 25 mg/kg) after oral administration. Based on these favorable biol. properties, RWJ 67657 may have use as a treatment for inflammatory diseases.

IT **215303-72-3**, RWJ 67657
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(RWJ 67657: potent oral inhibitor of p38 mitogen-activated protein kinase)

RN 215303-72-3 HCAPLUS
CN 3-Butyn-1-ol, 4-[4-(4-fluorophenyl)-1-(3-phenylpropyl)-5-(4-pyridinyl)-1H-imidazol-2-yl]- (9CI) (CA INDEX NAME)



102 Elected Species claim 16 not allowable

REFERENCE COUNT: 31 THERE ARE 31 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 2 OF 2 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text | Citing References

ACCESSION NUMBER: 1998:709071 HCAPLUS
DOCUMENT NUMBER: 129:330728
TITLE: Preparation of substituted imidazoles useful in the treatment of inflammatory diseases
INVENTOR(S): Beers, Scott A.; Malloy, Elizabeth; Wachter, Michael P.; **Wu, Wei**
PATENT ASSIGNEE(S): Ortho-McNeil Corporation, Inc., USA
SOURCE: PCT Int. Appl., 50 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

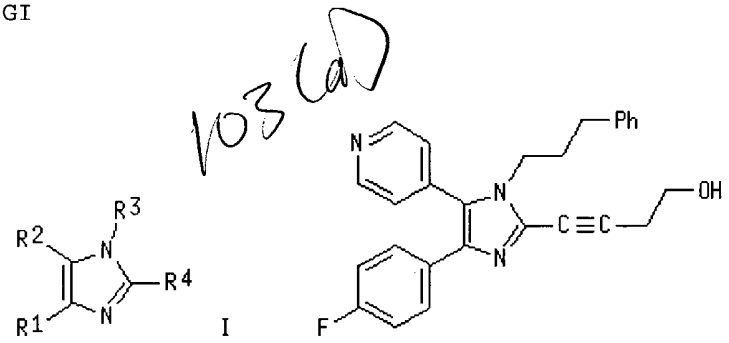
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9847892	A1	19981029	WO 1998-US7910	19980417
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
AU 9871382	A1	19981113	AU 1998-71382	19980417
US 5965583	A	19991012	US 1998-62304	19980417
TR 9902622	T2	20000522	TR 1999-9902622	19980417
BR 9808998	A	20000808	BR 1998-8998	19980417
EP 1028954	A1	20000823	EP 1998-918463	19980417
EP 1028954	B1	20030702		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
NZ 500447	A	20010928	NZ 1998-500447	19980417
JP 2001522357	T2	20011113	JP 1998-546231	19980417
AT 244234	E	20030715	AT 1998-918463	19980417
PT 1028954	T	20031128	PT 1998-918463	19980417
RU 2222534	C2	20040127	RU 1999-122164	19980417
ES 2202840	T3	20040401	ES 1998-918463	19980417
ZA 9803451	A	19991025	ZA 1998-3451	19980423
US 6214830	B1	20010410	US 1999-295156	19990420
NO 9905095	A	19991209	NO 1999-5095	19991019
MX 9909811	A	20000731	MX 1999-9811	19991025
US 6521655	B1	20030218	US 2000-705508	20001103

PRIORITY APPLN. INFO.:		
US 1997-44252P	P	19970424
US 1998-62304	A3	19980417

WO 1998-US7910 W 19980417
US 1999-295156 A3 19990420

OTHER SOURCE(S): MARPAT 129:330728

GI



I II

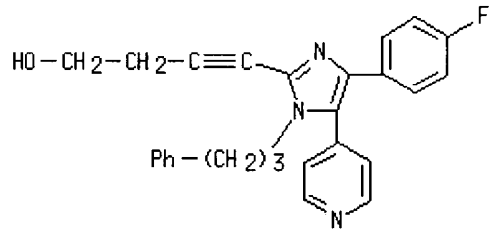
AB The title compds. [I; R1 = (un)substituted Ph, 5-6 membered heteroaryl; R2 = (un)substituted Ph, 5-6 membered heteroaryl; R3 = H, SEM, aryloxycarbonyl, etc.; R4 = A-(CH2)qX (wherein A = vinylene, ethynylene, C(:NOR5); R5 = H, C1-5 alkyl, Ph, Ph(C1-5 alkyl); q = 0-9; X = H, OH, vinyl, etc.); with the proviso that if A = C(:NOR5), q = 0 and X = H, R3 may not be SEM] which inhibit the prodn. of a no. of inflammatory cytokines, and are useful in the treatment of diseases assocd. with overprodn. of inflammatory cytokines, were prepd. Thus, coupling 4-(4-fluorophenyl)-2-iodo-1-(3-phenylpropyl)-5-(4-pyridyl)imidazole with 3-butyn-1-ol in the presence of Et3N and Pd(II)(PPh3)2(OAc)2 in CH2Cl2 afforded the title compd. II which showed IC50 of 7 nM against the prodn. of IL-1β and IC50 of 3.0 nM against TNF-α prodn.

IT **215303-72-3P**

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(prepn. of substituted imidazoles for the treatment of inflammatory diseases)

RN 215303-72-3 HCAPLUS

CN 3-Butyn-1-ol, 4-[4-(4-fluorophenyl)-1-(3-phenylpropyl)-5-(4-pyridinyl)-1H-imidazol-2-yl]- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> d his

(FILE 'HOME' ENTERED AT 19:45:07 ON 01 JUL 2004)

FILE 'REGISTRY' ENTERED AT 19:45:15 ON 01 JUL 2004

L1 STRUCTURE UPLOADED
L2 2 S L1
L3 35 S L1 FULL

```
     FILE 'HCAPLUS' ENTERED AT 19:49:05 ON 01 JUL 2004
L4            16 S L3
L5             0 S L4 AND BURNETT, D?/AU
L6             0 S L4 AND CAPLEN, M?/AU
L7             0 S L4 AND CZARNIECKI, M?/AU
L8             0 S L4 AND DOMALKSI, M?/AU
L9             0 S L4 AND HO, G?/AU
L10           46 S TULSHIAN, D?/AU
L11            0 S L10 AND L4
L12            2 S L4 AND WU, W?/AU

=> s l4 not l2
       1264343 l2
L13           13 L4 NOT l2

=> d l13, ibib abs fhitstr, 1-13

L13  ANSWER 1 OF 13  HCAPLUS  COPYRIGHT 2004 ACS on STN
```

Full Text | Citing References

ACCESSION NUMBER: 2003:998114 HCAPLUS
DOCUMENT NUMBER: 140:22524
TITLE: Therapy for chronic obstructive pulmonary disease in the 21st century
AUTHOR(S): Donnelly, Louise E.; Rogers, Duncan F.
CORPORATE SOURCE: Thoracic Medicine, National Hearth & Lung Institute, Imperial College, London, UK
SOURCE: Drugs (2003), 63(19), 1973-1998
CODEN: DRUGAY; ISSN: 0012-6667
PUBLISHER: Adis International Ltd.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

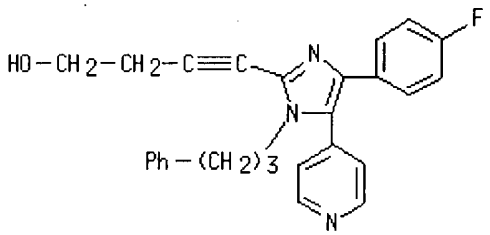
AB A review. Chronic obstructive pulmonary disease (COPD) is a common, smoking-related, severe respiratory condition characterized by progressive, irreversible airflow limitation. Current treatment of COPD is symptomatic, with no drugs capable of halting the relentless progression of airflow obstruction. Better understanding of the airway inflammation, oxidative stress and alveolar destruction that characterize COPD has delineated new disease targets, with consequent identification of novel compds. with therapeutic potential. These new drugs include aids to smoking cessation (e.g. bupropion) and improvements to existing therapies, for example long-acting rather than short-acting bronchodilators, as well as combination therapy. New antiproteases include acyl-enzyme and transition state inhibitors of neutrophil elastase (e.g. sivelestat and ONO-6818), matrix metalloprotease inhibitors (e.g. batimastat), cathepsin inhibitors and peptide protease inhibitors (e.g. DX-890 [EPI-HNE-4] and trappin-2). New antioxidants include superoxide dismutase mimetics (e.g. AEOL-10113) and spin trap compds. (e.g. N-tert-butyl-(α-phenylnitrone)). New anti-inflammatory interventions include phosphodiesterase-4 inhibitors (e.g. cilomilast), inhibitors of tumor necrosis factor-α (e.g. humanised monoclonal antibodies), adenosine A2a receptor agonists (e.g. CGS-21680), adhesion mol. inhibitors (e.g. bimosiamose [TBC1269]), inhibitors of nuclear factor-.vkappa.B (e.g. the naturally occurring compds. hypoestoxide and (-)-epigallocatechin-3-gallate) and activators of histone deacetylase (e.g. theophylline). There are also selective inhibitors of specific extracellular mediators such as chemokines (e.g. CXCR2 and CCR2 antagonists) and leukotriene B4 (e.g. SB201146), and of intracellular signal transduction mols. such as p38 mitogen activated protein kinase (e.g. RWJ67657) and phosphoinositide

3-kinase. Retinoids may be one of the few potential treatments capable of reversing alveolar destruction in COPD, and a no. of compds. are in clin. trial (e.g. all-trans-retinoic acid). Talniflumate (MSI-1995), an inhibitor of human calcium-activated chloride channels, has been developed to treat mucous hypersecretion. In addn., the purinoceptor P2Y2 receptor agonist diquafosol (INS365) is undergoing clin. trials to increase mucus clearance. The challenge to transferral of these new compds. from preclin. research to disease management is the design of effective clin. trials. The current scarcity of well characterized surrogate markers predicts that long-term studies in large nos. of patients will be needed to monitor changes in disease progression.

IT **215303-72-3**, RWJ67657
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(therapy for smoking-related chronic obstructive pulmonary disease)

RN 215303-72-3 HCAPLUS

CN 3-Butyn-1-ol, 4-[4-(4-fluorophenyl)-1-(3-phenylpropyl)-5-(4-pyridinyl)-1H-imidazol-2-yl]- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 205 THERE ARE 205 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 2 OF 13 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text | Citing References

ACCESSION NUMBER: 2003:308604 HCAPLUS
DOCUMENT NUMBER: 139:239612
TITLE: Single-dose pharmacokinetics and pharmacodynamics of RWJ 67657, a specific p38 mitogen-activated protein kinase inhibitor: a first-in-human study
AUTHOR(S): Parasrampuria, Dolly A.; de Boer, Peter; Desai-Krieger, Daksha; Chow, Andrew T.; Jones, C. Richard
CORPORATE SOURCE: Clinical Drug Evaluation, Johnson & Johnson Pharmaceutical R&D, Raritan, NJ, USA
SOURCE: Journal of Clinical Pharmacology (2003), 43(4), 406-413
CODEN: JCPCBR; ISSN: 0091-2700
PUBLISHER: Sage Publications
DOCUMENT TYPE: Journal
LANGUAGE: English

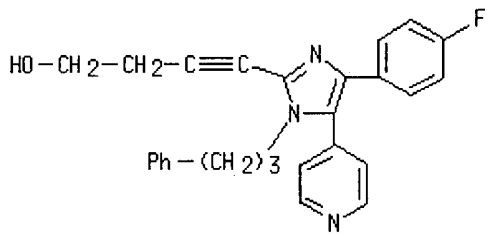
AB The objective of this study was to investigate the pharmacokinetics and ex vivo pharmacodynamics of increasing doses of RWJ 67657, along with the effect of food at one dose level in a first-in-human (FIH) study. This was a placebo-controlled, double-blind, randomized trial in healthy male subjects. Subjects received increasing doses of RWJ 67657 or placebo as a single oral dose (0.25-30 mg/kg) under fasting conditions. The effect of food was investigated for the 10-mg/kg dose. Plasma concns. of RWJ 67657 were measured over a period of 48 h using a validated LC-MS/MS method. To evaluate the pharmacodynamics of RWJ 67657, inhibition of cytokine prodn.

was monitored from ex vivo-stimulated polymorphonuclear blood cells (PBMCs). Pharmacokinetic/pharmacodynamic modeling was used to characterize the inhibitory activity of RWJ 67657. RWJ 67657 was rapidly absorbed (mean tmax = 0.6-2.5 h). The pharmacokinetics of RWJ 67657 appear to be nonlinear with respect to single-dose administration of the investigative formulation. Coadministration of food did not have a significant effect on half-life or time to peak concn. (tmax) but decreased the exposure. Mean Cmax values in the presence of food were almost 50% lower than during fasting (542 vs. 1283 ng/mL), and the AUC decreased from 2832 to 1904 ng·h/mL with food. RWJ 67657 inhibited TNF-α, IL-8, and IL-6 in a concn.-dependent manner with mean IC50 values of 0.18 μM, 0.04 μM, and 0.43 μM, resp. At 20 mg/kg, the median inhibition was greater than 85%. There were no significant adverse effects assocd. with single doses of this drug. This study demonstrates that RWJ 67657 has acceptable safety and pharmacokinetics to warrant further investigation in a repeat-dose setting. In addn., the early detn. of effect on biomarkers suggests potential efficacy in diseases mediated by proinflammatory and inflammatory cytokines.

IT **215303-72-3**, RWJ 67657
RL: PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(single-dose pharmacokinetics and pharmacodynamics of RWJ 67657)

RN 215303-72-3 HCAPLUS

CN 3-Butyn-1-ol, 4-[4-(4-fluorophenyl)-1-(3-phenylpropyl)-5-(4-pyridinyl)-1H-imidazol-2-yl]- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 14 THERE ARE 14 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

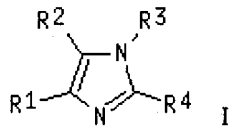
L13 ANSWER 3 OF 13 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text | Citing References

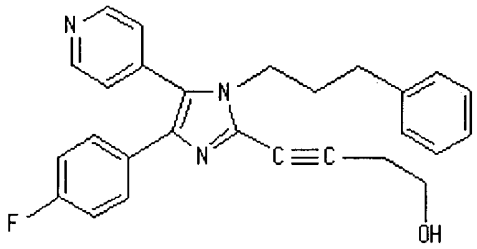
ACCESSION NUMBER: 2002:754379 HCAPLUS
DOCUMENT NUMBER: 137:263034
TITLE: Process for the preparation of tetrasubstituted imidazole derivatives and novel crystalline structures thereof
INVENTOR(S): Zhong, Hua; Dubberke, Silke; Muller, Stefan; Rossler, Armin; Schultz, Thomas W.; Korey, Daniel J.; Otten, Thomas; Walker, Donald G.; Abdel-Magid, Abdel
PATENT ASSIGNEE(S): Ortho-Mcneil Pharmaceutical, Inc., USA
SOURCE: PCT Int. Appl., 55 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE

WO 2002076974 A2 20021003 WO 2002-US5419 20020222
WO 2002076974 A3 20030213
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG
US 2003045723 A1 20030306 US 2002-81553 20020222
BR 2002008462 A 20040302 BR 2002-8462 20020222
EP 1392678 A2 20040303 EP 2002-753758 20020222
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR
PRIORITY APPLN. INFO.: US 2001-278607P P 20010326
US 2002-81553 A 20020222
WO 2002-US5419 W 20020222
OTHER SOURCE(S): CASREACT 137:263034; MARPAT 137:263034
GI



I

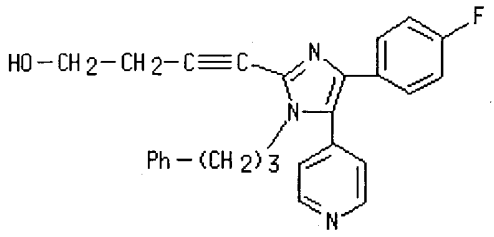


II

AB The present invention relates to a process for the prepn. of I [R1 = (un)substituted Ph; R2 = (un)substituted phenyl; R3 = H, aryl; R4 = C≡C(CH2)0-9-X; X = H, OH, vinyl, etc.]. For instance, the dimethoxy acetal of 4-pyridinecarboxaldehyde was lithiated (THF, n-BuLi, -15°) and added to the N-TMS-imine deriv. of 4-fluorobenzaldehyde (prepn. given) to afford 2,2-Dimethoxy-2-(4-pyridyl)-1-(4-fluorophenyl)ethanamine in 79% yield. This intermediate was acylated with N-(3-phenylpropyl)-1H-imidazole-1-carboxamide (prepn. given), to give the corresponding urea. This was treated with formic acid at 95-100° for 24 h resulting in hydrolysis of the ketal with concomitant cyclization to the corresponding imidazolin-2-one. The imidazolin-2-one was converted to the bromide (sulfolane, POBr3, 130°, 3 h, 62%) and subsequently coupled to 3-butyn-1-ol to give II in 75% yield. Two polymorphs of II were characterized by XRPD.

IT **215303-72-3P**, 4-(4-Fluorophenyl)-2-(4-hydroxy-1-butynyl)-1-(3-Phenylpropyl)-5-(4-Pyridyl)imidazole
RL: SPN (Synthetic preparation); PREP (Preparation)
(process for prepn. of tetrasubstituted imidazole derivs. and novel cryst. structures thereof)

RN 215303-72-3 HCAPLUS
CN 3-Butyn-1-ol, 4-[4-(4-fluorophenyl)-1-(3-phenylpropyl)-5-(4-pyridinyl)-1H-imidazol-2-yl]- (9CI) (CA INDEX NAME)



L13 ANSWER 4 OF 13 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text | Citing References

ACCESSION NUMBER: 2002:594816 HCAPLUS
DOCUMENT NUMBER: 137:135120
TITLE: Use of CSBP/p38 inhibitors for the treatment of inflammation-enhanced cough
INVENTOR(S): Griswold, Don E.; Underwood, David C.
PATENT ASSIGNEE(S): Smithkline Beecham Corporation, USA
SOURCE: PCT Int. Appl., 20 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

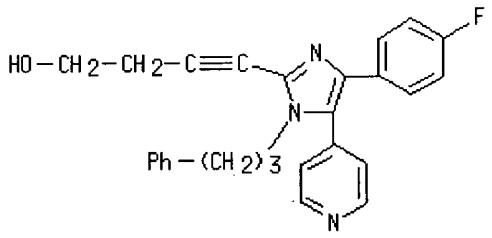
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002060869	A2	20020808	WO 2001-US50629	20011019
WO 2002060869	A3	20030103		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
EP 1337255	A2	20030827	EP 2001-997150	20011019
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
US 2004097473	A1	20040520	US 2003-399579	20030418

PRIORITY APPLN. INFO.: US 2000-241564P P 20001019
WO 2001-US50629 W 20011019

AB The invention discloses the use of a CSBP/p38 inhibitor for the treatment and prophylaxis of inflammation-enhanced cough in a mammal in need thereof.

IT **215303-72-3**, RWJ 67657
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(CSBP/p38 inhibitors for treatment of inflammation-enhanced cough)

RN 215303-72-3 HCAPLUS
CN 3-Butyn-1-ol, 4-[4-(4-fluorophenyl)-1-(3-phenylpropyl)-5-(4-pyridinyl)-1H-imidazol-2-yl]- (9CI) (CA INDEX NAME)



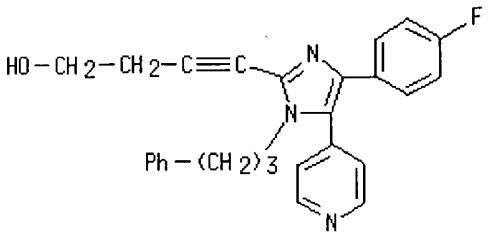
L13 ANSWER 5 OF 13 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text | Citing References

ACCESSION NUMBER: 2002:344594 HCAPLUS
DOCUMENT NUMBER: 137:345766
TITLE: Inhibition of p38 mitogen-activated protein kinase: dose-dependent suppression of leukocyte and endothelial response after endotoxin challenge in humans
AUTHOR(S): Fijen, Jan-Willem; Tulleken, Jaap E.; Kobold, Anneke C. Muller; de Boer, Peter; van der Werf, Tjip S.; Ligtenberg, Jack J. M.; Spanjersberg, Rob; Zijlstra, Jan G.
CORPORATE SOURCE: Intensive and Respiratory Care Unit, University Hospital Groningen, Groningen, Neth.
SOURCE: Critical Care Medicine (2002), 30(4), 841-845
CODEN: CCMDC7; ISSN: 0090-3493
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Objective: We studied the activity of a single oral dose of RWJ-67657, a synthetic p38 mitogen-activated protein kinase inhibitor, in preventing dual leukocyte/endothelial activation after endotoxin infusion in healthy volunteers. Design: Prospective placebo-controlled study. Setting: Intensive care unit at a university medical center. Subjects: Twenty-one healthy male volunteers. Interventions: Endotoxin (4 ng/kg) as a 1-min infusion. According to randomization, the volunteers received placebo (n = 6) or 1400 mg (n = 4), 700 mg (n = 6), or 350 mg (n = 5) of RWJ-67657. Measurements and Main Results: Neutrophil activation was investigated by analyzing the extent of membrane expression of adhesion markers by calibrated flow cytometry. Circulating intercellular adhesion mol.-1 and E-selectin were measured by enzyme-linked immunosorbent assays. The endotoxin-induced shedding of L-selectin was diminished in a dose-dependent manner ($p < .0001$). High-dose RWJ-67657 prevented up-regulation of the integrins CD11b ($p < .01$) and CD 66b ($p < .01$) on neutrophils. The endotoxin-induced increase in circulating intercellular adhesion mol.-1 and circulation E-selectin was almost completely prevented by high-dose RWJ-67657. Conclusion: A single oral dose of RWJ-67657 prevented neutrophil and endothelial activation after endotoxin infusion.

IT 215303-72-3, RWJ-67657
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(RWJ67657, p38 mitogen-activated protein kinase inhibitor, in preventing leukocyte/endothelial activation after endotoxin challenge in humans)
RN 215303-72-3 HCAPLUS
CN 3-Butyn-1-ol, 4-[4-(4-fluorophenyl)-1-(3-phenylpropyl)-5-(4-pyridinyl)-1H-imidazol-2-yl]- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 27 THERE ARE 27 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 6 OF 13 HCAPLUS COPYRIGHT 2004 ACS on STN

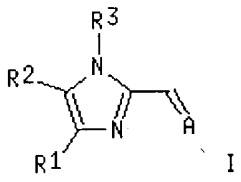
Full Text | Citing References

ACCESSION NUMBER: 2002:314935 HCAPLUS
DOCUMENT NUMBER: 136:325546
TITLE: Preparation of substituted imidazoles useful in the treatment of inflammatory diseases
INVENTOR(S): Beers, Scott; Wachter, Michael P.
PATENT ASSIGNEE(S): Ortho-McNeil Pharmaceutical, Inc., USA
SOURCE: PCT Int. Appl., 42 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002032894	A1	20020425	WO 2001-US32436	20011017
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2002024402	A5	20020429	AU 2002-24402	20011017
EP 1337526	A1	20030827	EP 2001-987750	20011017
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
JP 2004511554	T2	20040415	JP 2002-536276	20011017

PRIORITY APPLN. INFO.: US 2000-241256P P 20001018
WO 2001-US32436 W 20011017

OTHER SOURCE(S): MARPAT 136:325546
GI



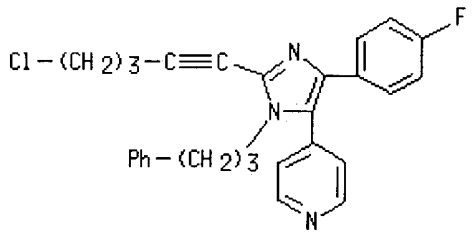
I

AB The title imidazoles I [R1 = Ph, heteroaryl; R2 = Ph, heteroaryl; R3 = H, alkyl, arylalkyl, aminoalkyl, etc.; A = seven member heterocyclyl ring] were prepd. E. g., 4-[4-(4-fluorophenyl)-2-[(E)-(1-methyl-2-pyrrolidinylidene)methyl]-1-(3-phenylpropyl)-1H-imidazol-5-yl]pyridine was prepd. The compds. of the invention modulate the prodn. of a no. of inflammatory cytokines and are useful in the treatment of diseases assocd. with the overpopulation of inflammatory cytokines.

IT 215303-87-0
RL: RCT (Reactant); RACT (Reactant or reagent)
(prepn. of substituted imidazoles useful in the treatment of inflammatory diseases)

RN 215303-87-0 HCAPLUS

CN Pyridine, 4-[2-(5-chloro-1-pentynyl)-4-(4-fluorophenyl)-1-(3-phenylpropyl)-1H-imidazol-5-yl]- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 7 OF 13 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text | Citing References

ACCESSION NUMBER: 2002:314904 HCAPLUS
DOCUMENT NUMBER: 136:319434
TITLE: Use of p38 inhibitors for the treatment of smoke inhalation
INVENTOR(S): Griswold, Don E.; Underwood, David C.
PATENT ASSIGNEE(S): Smithkline Beecham Corporation, USA
SOURCE: PCT Int. Appl., 15 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002032862	A2	20020425	WO 2001-US50429	20011019
WO 2002032862	A3	20020822		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
EP 1337250	A2	20030827	EP 2001-987743	20011019
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
JP 2004511542	T2	20040415	JP 2002-536046	20011019

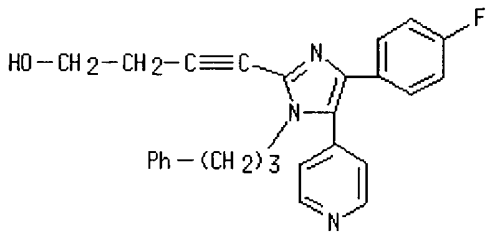
US 2004092532 A1 20040513 US 2003-399580 20030418
PRIORITY APPLN. INFO.: US 2000-241568P P 20001019
WO 2001-US50429 W 20011019

AB The present invention is directed to the novel use of a CSBP/p38 inhibitor for the treatment, including prophylaxis of smoke induced pathol. resulting from acute and chronic inflammation in the lung. In the example provided, the p38 MAP kinase inhibitor trans-1-(4-hydroxycyclohexyl)-4-(4-fluorophenyl)-5-[(2-methoxy)pyrimidin-4-yl]imidazole inhibited airway inflammation caused by tobacco smoke inhalation in mice. The p38 MAP kinase inhibitors are also useful in inflammations caused by other types of smoke and in such inflammations exacerbated by underlying conditions such as asthma and pneumonia.

IT **215303-72-3**, RWJ 67657
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(use of p38 inhibitors combined with other agents for treatment of airway inflammation from smoke inhalation)

RN 215303-72-3 HCAPLUS

CN 3-Butyn-1-ol, 4-[4-(4-fluorophenyl)-1-(3-phenylpropyl)-5-(4-pyridinyl)-1H-imidazol-2-yl]- (9CI) (CA INDEX NAME)



L13 ANSWER 8 OF 13 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text | Citing References

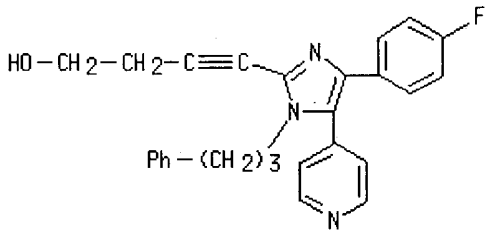
ACCESSION NUMBER: 2001:858511 HCAPLUS
DOCUMENT NUMBER: 136:130624
TITLE: Kinetics of small molecule inhibitor binding to p38 kinase
AUTHOR(S): Thurmond, Robin L.; Wadsworth, Scott A.; Schafer, Peter H.; Zivin, Robert A.; Siekierka, John J.
CORPORATE SOURCE: R.W. Johnson Pharmaceutical Research Institute, San Diego, CA, 92121, USA
SOURCE: European Journal of Biochemistry (2001), 268(22), 5747-5754
CODEN: EJBCAI; ISSN: 0014-2956
PUBLISHER: Blackwell Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB P38 mitogen-activated protein kinase (MAPK) (p38/p38-α/CSBP2/RK) has been implicated in the regulation of many pro-inflammatory pathways. Because of this, it has received much attention as a potential drug target for controlling diseases such as rheumatoid arthritis, endotoxic shock, inflammatory bowel disease, osteoporosis, and many others. A no. of small mol. inhibitors of this kinase have been described, and in this paper we have used surface plasmon resonance to directly measure and quantitate their binding to p38. Despite the relatively low mol. mass (≈ 400 Da) of these inhibitors, specific binding can be obsd. For the two most potent inhibitors studied, SB 203580 and RWJ 67657, dissocn. consts., Kd's, of 22 and 10 nM, resp., were obtained. These values closely match the IC50 values obsd. in a cell-based TNFα release assay implying

that p38 plays a major role in TNFα release. The assocn. and dissocn. rates for the binding of these inhibitors to p38 have also been quantitated. SB 203580 and RWJ 67657 have very similar assocn. rates of around 8 105 ı M-1 ·s-1, and the differences in affinity are detd. by different dissocn. rates. The weaker binding compds. have dissocn. rates similar to SB 203580, but the assocn. rates vary by an order of magnitude or more. The direct measurement of compds. binding to p38 may help in understanding the difference between potency and efficacy for these inhibitors. This in turn may yield clues on how to develop better inhibitors.

IT **215303-72-3**, RWJ 67657
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(RWJ 67657; kinetics of small mol. inhibitor binding to p38 kinase)

RN 215303-72-3 HCAPLUS
CN 3-Butyn-1-ol, 4-[4-(4-fluorophenyl)-1-(3-phenylpropyl)-5-(4-pyridinyl)-1H-imidazol-2-yl]- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 9 OF 13 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text | Citing References

ACCESSION NUMBER: 2001:672214 HCAPLUS
DOCUMENT NUMBER: 135:221314
TITLE: Use of kinase inhibitors for treating neurodegenerative diseases
INVENTOR(S): Zawada, Michael; Heidenreich, Kim; Freed, Curt
PATENT ASSIGNEE(S): USA
SOURCE: U.S., 36 pp.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 6288089	B1	20010911	US 1999-469980	19991221

PRIORITY APPLN. INFO.: US 1998-113263P P 19981221

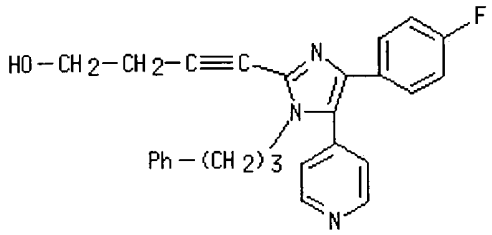
AB Methods are provided for treating neurodegenerative diseases, including but not limited to Parkinson's disease. In particular, the invention provides methods using the administration of pyridyl imidazoles having simultaneous inhibitory activity towards p38 mitogen-activated protein (MAP) kinase and c-jun-N-terminal kinase (JNK). The invention also provides methods for preventing apoptosis of dopamine neurons using pyridyl imidazoles. The invention further provides methods for the treatment of neurodegenerative diseases, including but not limited to Parkinson's disease.

IT **215303-72-3**, RWJ 67657

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(kinase inhibitors for treating neurodegenerative diseases)

RN 215303-72-3 HCAPLUS

CN 3-Butyn-1-ol, 4-[4-(4-fluorophenyl)-1-(3-phenylpropyl)-5-(4-pyridinyl)-1H-imidazol-2-yl]- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 10 OF 13 HCAPLUS COPYRIGHT 2004 ACS on STN

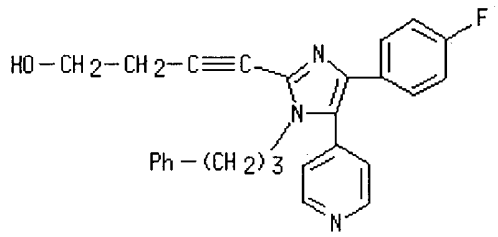
Full Text | Citing References

ACCESSION NUMBER: 2001:439750 HCAPLUS
DOCUMENT NUMBER: 136:193857
TITLE: Suppression of the clinical and cytokine response to endotoxin by RWJ-67657, a p38 mitogen-activated protein-kinase inhibitor, in healthy human volunteers
AUTHOR(S): Fijen, J. W.; Zijlstra, J. G.; De Boer, P.; Spanjersberg, R.; Tervaert, J. W. Cohen; Van Der Werf, T. S.; Ligtenberg, J. J. M.; Tulleken, J. E.
CORPORATE SOURCE: Intensive and Respiratory Care Unit, University Hospital, Groningen, 9700 RB, Neth.
SOURCE: Clinical and Experimental Immunology (2001), 124(1), 16-20
CODEN: CEXIAL; ISSN: 0009-9104
PUBLISHER: Blackwell Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Sepsis resulting in multiorgan failure and death is still a major problem in intensive care medicine, despite extensive attempts to interfere in the supposed underlying mechanism of a deranged immune system. This is not only due to the persistent lacunae in knowledge about the immune system in sepsis but also due to the lack of sufficient instruments for intervention. Inhibitors of the p38 mitogen-activated protein kinase (p38MAPK) have been used to study the signalling pathway of the immune response. In vitro and animal studies have demonstrated that blocking p38MAPK could mitigate the pro-inflammatory response and improve survival after endotoxemia. Using an endotoxemia model in healthy human volunteers, the authors evaluated the attenuation of clin. and cytokine response to endotoxin after inhibition of p38MAPK by an oral dose of RWJ-67657, a pyrindinyl imidazole. They measured the clin. parameters temp., blood pressure, and heart rate. The proinflammatory cytokines tumor necrosis factor α, interleukin 6, and interleukin 8 were measured by ELISA at various points during a 24-h period. Drug toxicity was evaluated by routine clin. and lab. examns. After a single dose of RWJ-67657, the temp. and blood pressure response remained at the basal level. The inhibition of TNF α, IL 6, and IL 8 response was dose-dependent. With the max. dosage, redn. in peak serum levels of the

proinflammatory cytokines was >90%. There was no drug-related toxicity. Interpretation: Inhibition of p38MAPK by RWJ-67657 might be a tool to intervene in the deranged immune response in sepsis and other inflammatory diseases.

IT 215303-72-3, RWJ-67657
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(suppression of clin. and cytokine response to endotoxin by RWJ-67657 in humans)
RN 215303-72-3 HCAPLUS
CN 3-Butyn-1-ol, 4-[4-(4-fluorophenyl)-1-(3-phenylpropyl)-5-(4-pyridinyl)-1H-imidazol-2-yl]- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 27 THERE ARE 27 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 11 OF 13 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text | Citing References

ACCESSION NUMBER: 2001:208067 HCAPLUS
DOCUMENT NUMBER: 134:242657
TITLE: Use of CSAIDs (cytokine suppressive antiinflammatory drugs) in rhinovirus infection
INVENTOR(S): Dillon, Susan B.; Griego, Sandra D.
PATENT ASSIGNEE(S): Smithkline Beecham Corp., USA
SOURCE: PCT Int. Appl., 30 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001019322	A2	20010322	WO 2000-US25386	20000915
WO 2001019322	A3	20011004		
W: AE, AL, AU, BA, BB, BG, BR, BZ, CA, CN, CZ, DZ, EE, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KP, KR, LC, LK, LR, LT, LV, MA, MG, MK, MN, MX, MZ, NO, NZ, PL, RO, SG, SI, SK, SL, TR, TT, TZ, UA, US, UZ, VN, YU, ZA, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 2000075845	A5	20010417	AU 2000-75845	20000915
EP 1223924	A2	20020724	EP 2000-965060	20000915
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL				
TR 200200673	T2	20021223	TR 2002-20020067	20000915
JP 2003516314	T2	20030513	JP 2001-522960	20000915
BR 2000014041	A	20030715	BR 2000-14041	20000915
ZA 2002002060	A	20030312	ZA 2002-2060	20020313
NO 2002001301	A	20020516	NO 2002-1301	20020315

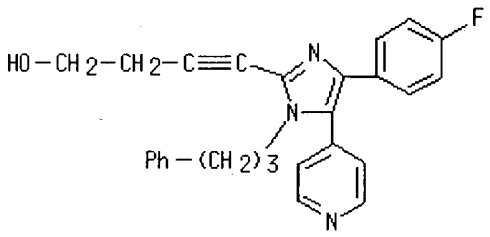
PRIORITY APPLN. INFO.: US 1999-154494P P 19990917
WO 2000-US25386 W 20000915

AB The present invention is directed to the novel use of a CSBP/p38 kinase inhibitor for the treatment of symptoms of the common cold and the exacerbation of symptoms assocd. therewith in humans. The effect of a compd. trans-1-(4-hydroxycyclohexyl)-4-(4-fluorophenyl)-5-[(2-methoxy)pyrimidin-4-yl]imidazole on the rhinovirus-induced cytokine prodn. by epithelial cells was examd.

IT **215303-72-3**, RWJ 67657
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(cytokine suppressive antiinflammatory drugs (CSAIDs) for treatment of rhinovirus infection)

RN 215303-72-3 HCAPLUS

CN 3-Butyn-1-ol, 4-[4-(4-fluorophenyl)-1-(3-phenylpropyl)-5-(4-pyridinyl)-1H-imidazol-2-yl]- (9CI) (CA INDEX NAME)



L13 ANSWER 12 OF 13 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text | Citing References

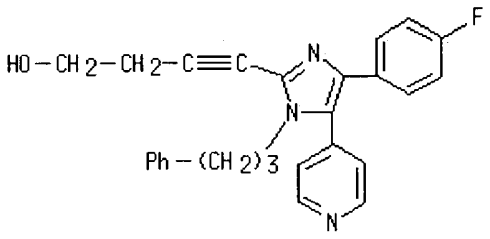
ACCESSION NUMBER: 1999:714273 HCAPLUS
DOCUMENT NUMBER: 132:30503
TITLE: RWJ 67657, a potent, orally active inhibitor of p38 mitogen-activated protein kinase
AUTHOR(S): Wadsworth, Scott A.; Cavender, Druie E.; Beers, Scott A.; Lalan, Praful; Schafer, Peter H.; Malloy, Elizabeth A.; Wu, Wei; Fahmy, Bohumila; Olini, Gilbert C.; Davis, Janet E.; Pellegrino-Gensey, J. Lee; Wachter, Michael P.; Siekierka, John J.
CORPORATE SOURCE: Drug Discovery, The R. W. Johnson Pharmaceutical Research Institute, Raritan, NJ, USA
SOURCE: Journal of Pharmacology and Experimental Therapeutics (1999), 291(2), 680-687
CODEN: JPETAB; ISSN: 0022-3565
PUBLISHER: American Society for Pharmacology and Experimental Therapeutics
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Tumor necrosis factor-α (TNF-α), a cytokine secreted by activated monocytes/macrophages and T lymphocytes, has been implicated in several disease states, including rheumatoid arthritis, inflammatory bowel disease, septic shock, and osteoporosis. Monocyte/macrophage prodn. of TNF-α is dependent on the mitogen-activated protein kinase p38. RWJ 67657 (4-[4-(4-fluorophenyl)-1-(3-phenylpropyl)-5-(4-pyridinyl)-1H-imidazol -2-yl]-3-butyn-1-ol) inhibited the release of TNF-α by lipopolysaccharide (a monocyte stimulus)-treated human peripheral blood mononuclear cells with an IC50 of 3 nM, as well as the release of TNF-α from peripheral blood mononuclear cells treated with the superantigen staphylococcal enterotoxin B (a T cell stimulus), with an IC50 value of 13 nM. This compd. was approx. 10-fold more potent than the

literature std. p38 kinase inhibitor SB 203580 in all p38 dependent in vitro systems tested. RWJ 67657 inhibited the enzymic activity of recombinant p38α and β, but not γ or δ, in vitro and had no significant activity against a variety of other enzymes. In contrast, SB 203580 significantly inhibited the tyrosine kinases p56 lck and c-src (IC50 = 5 μM). RWJ 67657 did not inhibit T cell prodn. of interleukin-2 or interferon-γ and did not inhibit T cell proliferation in response to mitogens. RWJ 67657 inhibited TNF-α prodn. in lipopolysaccharide-injected mice (87% inhibition at 50 mg/kg) and in rats (91% inhibition at 25 mg/kg) after oral administration. Based on these favorable biol. properties, RWJ 67657 may have use as a treatment for inflammatory diseases.

IT 215303-72-3, RWJ 67657
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(RWJ 67657: potent oral inhibitor of p38 mitogen-activated protein kinase)

RN 215303-72-3 HCAPLUS
CN 3-Butyn-1-ol, 4-[4-(4-fluorophenyl)-1-(3-phenylpropyl)-5-(4-pyridinyl)-1H-imidazol-2-yl]- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 31 THERE ARE 31 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 13 OF 13 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text | Citing References

ACCESSION NUMBER: 1998:709071 HCAPLUS
DOCUMENT NUMBER: 129:330728
TITLE: Preparation of substituted imidazoles useful in the treatment of inflammatory diseases
INVENTOR(S): Beers, Scott A.; Malloy, Elizabeth; Wachter, Michael P.; Wu, Wei
PATENT ASSIGNEE(S): Ortho-McNeil Corporation, Inc., USA
SOURCE: PCT Int. Appl., 50 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9847892	A1	19981029	WO 1998-US7910	19980417

W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG

AU 9871382	A1	19981113	AU 1998-71382	19980417
US 5965583	A	19991012	US 1998-62304	19980417
TR 9902622	T2	20000522	TR 1999-9902622	19980417
BR 9808998	A	20000808	BR 1998-8998	19980417
EP 1028954	A1	20000823	EP 1998-918463	19980417
EP 1028954	B1	20030702		

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI

NZ 500447	A	20010928	NZ 1998-500447	19980417
JP 2001522357	T2	20011113	JP 1998-546231	19980417
AT 244234	E	20030715	AT 1998-918463	19980417
PT 1028954	T	20031128	PT 1998-918463	19980417
RU 2222534	C2	20040127	RU 1999-122164	19980417
ES 2202840	T3	20040401	ES 1998-918463	19980417
ZA 9803451	A	19991025	ZA 1998-3451	19980423
US 6214830	B1	20010410	US 1999-295156	19990420
NO 9905095	A	19991209	NO 1999-5095	19991019
MX 9909811	A	20000731	MX 1999-9811	19991025
US 6521655	B1	20030218	US 2000-705508	20001103

PRIORITY APPLN. INFO.:

US 1997-44252P	P	19970424
US 1998-62304	A3	19980417
WO 1998-US7910	W	19980417
US 1999-295156	A3	19990420

OTHER SOURCE(S): MARPAT 129:330728

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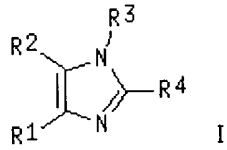

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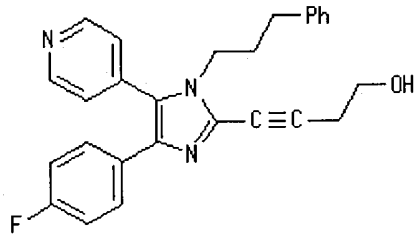


II

AB The title compds. [I; R1 = (un)substituted Ph, 5-6 membered heteroaryl; R2 = (un)substituted Ph, 5-6 membered heteroaryl; R3 = H, SEM, aryloxycarbonyl, etc.; R4 = A-(CH2)qX (wherein A = vinylene, ethynylene, C(:NOR5); R5 = H, C1-5 alkyl, Ph, Ph(C1-5 alkyl); q = 0-9; X = H, OH, vinyl, etc.); with the proviso that if A = C(:NOR5), q = 0 and X = H, R3 may not be SEM] which inhibit the prodn. of a no. of inflammatory cytokines, and are useful in the treatment of diseases assocd. with overprodn. of inflammatory cytokines, were prepd. Thus, coupling 4-(4-fluorophenyl)-2-iodo-1-(3-phenylpropyl)-5-(4-pyridyl)imidazole with 3-butyn-1-ol in the presence of Et3N and Pd(II)(PPh3)2(OAc)2 in CH2Cl2 afforded the title compd. II which showed IC50 of 7 nM against the prodn. of IL-1β and IC50 of 3.0 nM against TNF-α prodn.

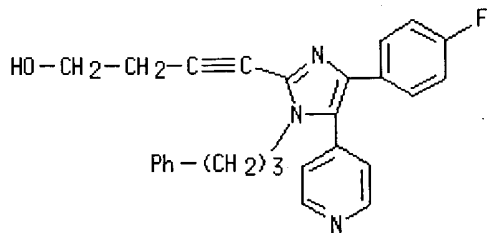
IT **215303-72-3P**

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)

(prepn. of substituted imidazoles for the treatment of inflammatory diseases)

RN 215303-72-3 HCAPLUS

CN 3-Butyn-1-ol, 4-[4-(4-fluorophenyl)-1-(3-phenylpropyl)-5-(4-pyridinyl)-1H-imidazol-2-yl]- (9CI) (CA INDEX NAME)



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FULL ESTIMATED COST	85.50	243.23

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	-10.40	-10.40

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FILE LAST UPDATED: 01 May 1997 (19970501/UP)

This file contains CAS Registry Numbers for easy and accurate substance identification. Title keywords, authors, patent assignees, and patent information, e.g., patent numbers, are now searchable from 1907-1966. TIFF images of CA abstracts printed between 1907-1966 are available in the PAGE display formats.

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L5 0 S L4 AND BURNETT, D?/AU
L6 0 S L4 AND CAPLEN, M?/AU
L7 0 S L4 AND CZARNIECKI, M?/AU
L8 0 S L4 AND DOMALKSI, M?/AU
L9 0 S L4 AND HO, G?/AU

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L12            2 S L4 AND WU, W?/AU
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